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Structural Feature Identification of Amidinophenylurea Derivatives for Factor VIIa Inhibition

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ABSTRACT: We describe the 3D QSAR and pharmacophore identification on 28 reported factor VIIa inhibitors. The QSAR and pharmacophore identification studies exhibited the significance of amidine group for factor VIIa inhibition.

KEYWORDS: Factor VIIa; Anticoagulant; 3D QSAR; Vlife MDS; Amidine.

Introduction

Factor VIIa along with tissue factor starts whole coagulation process, so factor VIIa is acting as attractive target for anticoagulant drug design. The inhibition of factor VIIa can result in inhibition of coagulation in the early stages. The factor VIIa inhibitors can act more potent antithrombotic than factor Xa inhibitors. Variety of factor VIIa inhibitors are reported by the various researchers. It is necessary to indentify the structural requirements which are required for factor VIIa inhibition, which can be achieved by the QSAR and pharmacophore identification studies. The QSAR studies correlate the structural properties with the biological activity which gives idea about the significant properties and non significant properties for desired pharmacological activity. The pharmacophore is nothing but the molecular framework which is having the desired features which are essential for activity. Current manuscript deals with the 3D QSAR by PLS method and pharmacophore identification studies on 28 reported factor VIIa inhibitors. The QSAR model and pharmacophoric hypothesis can be utilised for designing of more potent factor VIIa inhibitors[1-7].

Experimental Procedure

Computational details

A dataset of 33 compounds was taken from the published factor VIIa inhibitors by Klingler et.al.,[8] (Table no 1). The whole dataset was randomly divided into a training set of 22 compounds and a test set 06 of compounds (asterisked molecules in Table 1).

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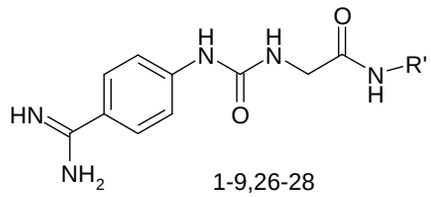
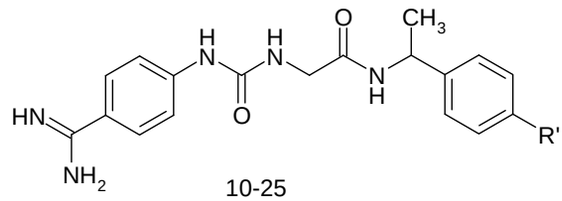
Table 1 Table showing molecules under study



1-9,26-28



10-25

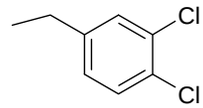
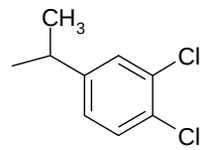
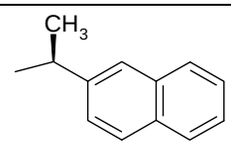
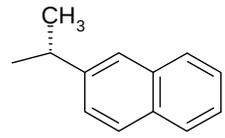
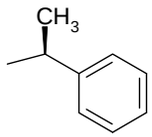
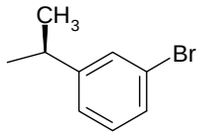
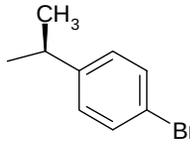
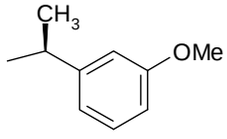
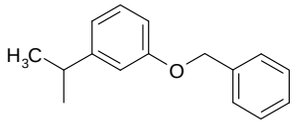
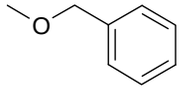
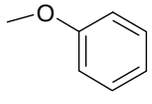
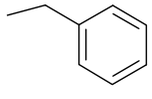
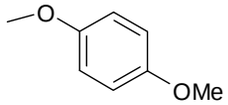
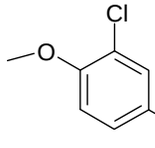
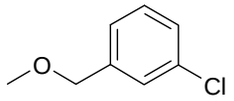
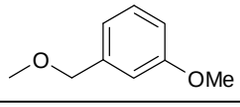
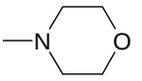
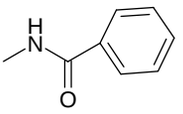
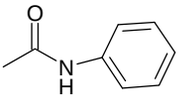
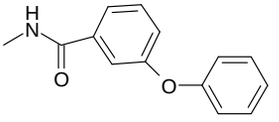
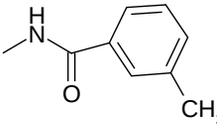
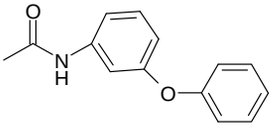
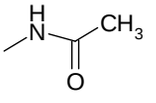
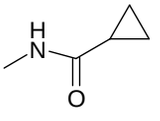
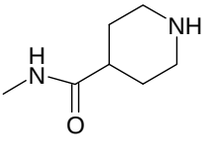
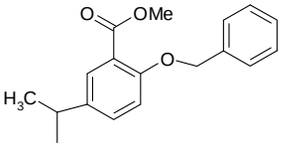
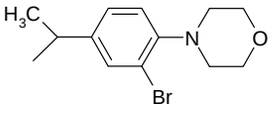
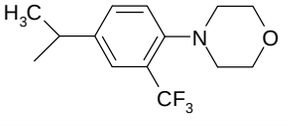
Sr. no.	R'	Observed activity	Predicted activity
1.		0.97	0.90
2.		0.077	0.05132
3.		0.026	0.034665
4.		7	7.62

Table 1 *Contd…*

Sr. no.	R'	Observed activity	Predicted activity
5.		0.43	0.349
6.		0.027	0.0255
7.		0.156	0.154
8.		0.035	0.002
9.		0.256	0.272
10.		0.133	0.101
11.		0.078	0.072
12.		0.19	0.184
13.		0.083	0.0811
14.		0.483	0.520
15.		0.023	0.002
16.		0.02	0.022
17.		0.142	0.072
18.		0.034	-0.003
19.		0.02	0.186
20.		0.012	0.012
21.		0.026	0.048
22.		0.043	0.0663
23.		0.196	0.238
24.		0.047	0.057
25.		0.013	0.013
26.		0.033	0.043
27.		0.015	0.011
28.		0.03	0.022

Materials and Methods

The structure of Amidinophenylurea was used as template to built the molecules in the dataset in Vlife MDS 3.5 and then minimized using the Merk molecular force field.

Molecular alignment

The molecules of the dataset were aligned by the template based technique, using common structure of amidino-phenylurea. The alignment of all the molecules on the template is shown in Figure 1.

Descriptor calculation

3D descriptors are nothing but the hydrophilic, steric and electrostatic interaction energies which are computed at the lattice points of the grid using a methyl probe of charge +1.

3D QSAR studies using partial least squares regression

The relationship between the biological activity and 3D descriptors is carried out in QSAR module of Vlife MDS 3.5. The generated models are selected using various statistical parameters like r^2, q^2, f values. Thus models having correlation coefficient above 0.7 were used to check the external predictivity while the significance of the model was decided on the basis of F value. Models showing q^2 below 0.6 were discarded. The selected models are shown in Table 2. (Figure 2).

Pharmacophore modeling

Pharmacophore modelling was carried out using the Mol sign module of Vlife Mds 3.5 software. The software was set to generate minimum 4 pharmacophoric features obtained keeping the tolerance limit at 10 A^0.

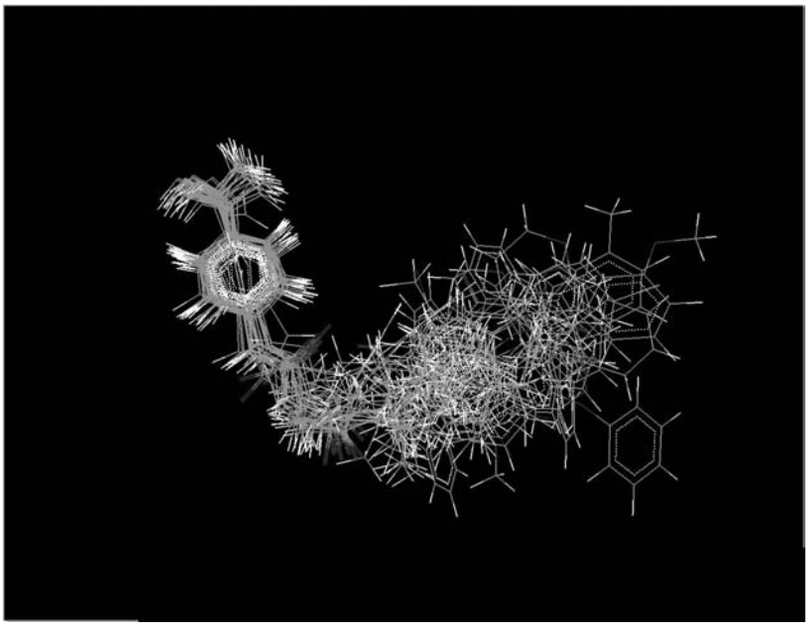


Fig. 1 Figure showing the alignment of the molecules.

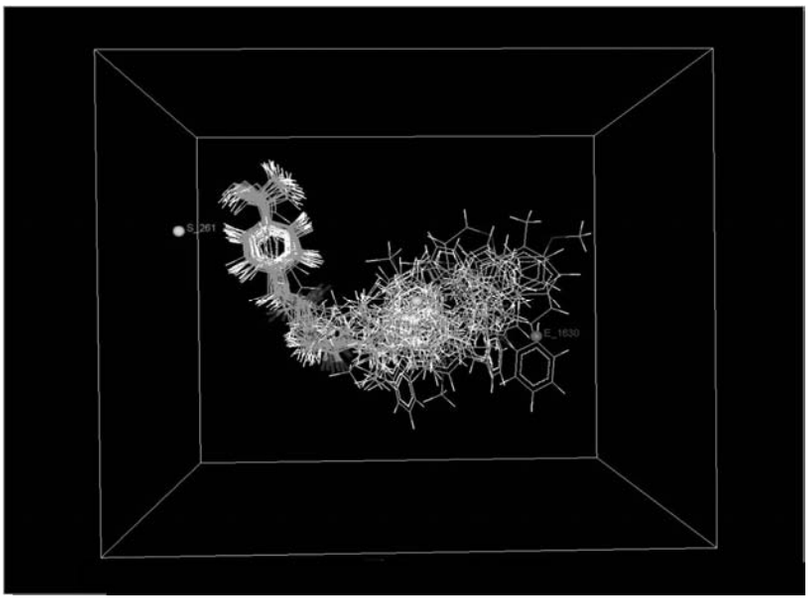


Fig. 2 Figure showing the field point of selected QSAR model A.

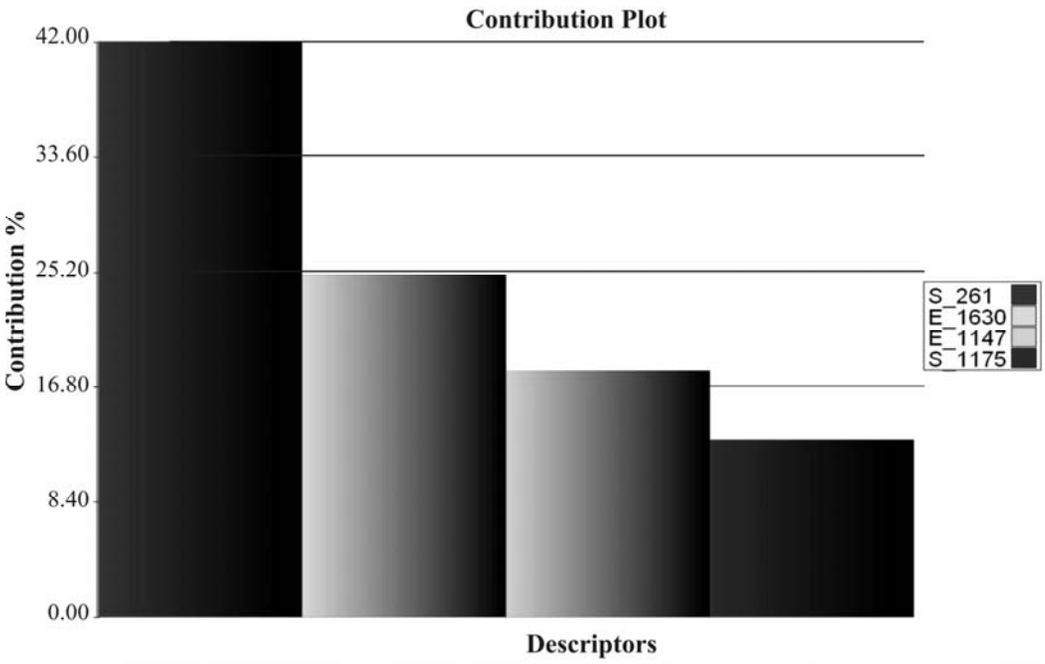


Fig. 3 Figure showing contribution plot of selected QSAR model A.

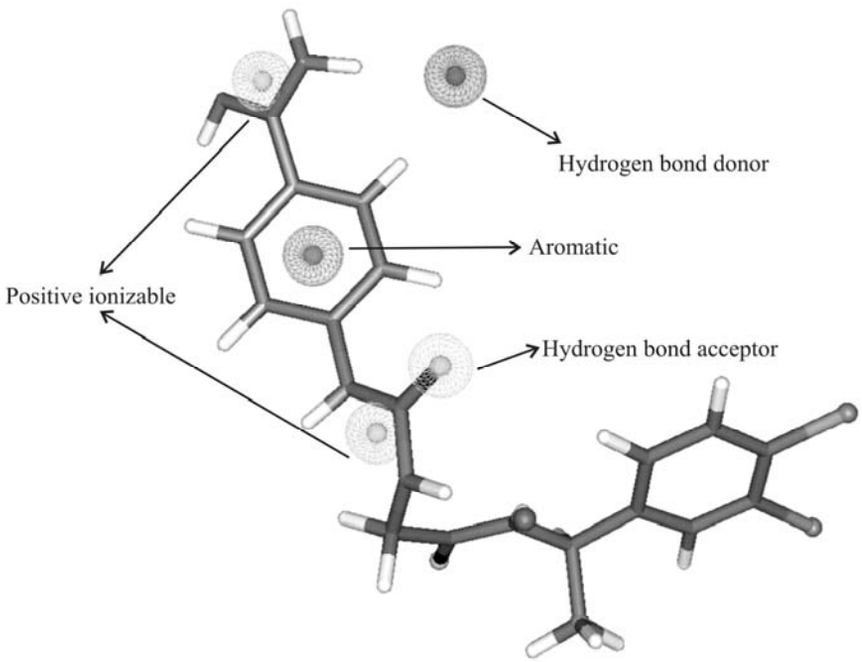


Fig. 4 Figure showing selected pharmacophore model gene-rated through Vlife MDS.

Results and Discussion

In the present study, 22 molecules were used in the training set (Table 1) to derive 3D QSAR models with the number of field grid points being not more than five per model. To evaluate the predictive ability of generated 3D-QSAR models, and test set of 08 molecules with regularly distributed biological activities was used (Table 1). The model selected after the successful run of PLS is given in Table 2.

Table 2 Table showing the selected MLR QSAR equations along with statistical parameters employed for model selection

Model No.	QSAR model	N	r^2	q^2	F value	Pred r^2
A	Ki = 0.0081 + 0.0481 S_261 + 0.0163 E_1630 + 0.0078 E_1147 + 0.0033 S_1175	28	0.98	0.92	52.12	0.84

Interpretation of 3QSAR model

The model A is selected on the basis of its statistical coefficient like r^2 (0.9878) and Pred r^2 (0.8491). The contributing descriptor for model A is S_261, E_1630, E_1147 and S_1175. The electrostatic interaction at lattice point E_1630 and E_1147 are positively contributing means substitution of electron releasing groups will be increasing the inhibitory potential of the molecules (Fig. 3). Also the steric interaction at the lattice point S_261 and S_1175 is positively contributing, so substation of bulkier groups will be increasing the activity.

Pharmacophore identification studies using Vlife MDS 3.5

A set of pharmacophore hypothesis was generated using the mole sign module of Vlife MDS 3.5. The each hypothesis was found to contain common features like hydrogen bond doner, hydrogen bond acceptor, aromatic and positive ionizable. The pharmacophore hypothesis generated in Vlife MDS 3.5 (Figure 4) indicated that hydrogen bond donor and hydrogen bond acceptor, aromatic and two positive ionizable features are required for factor VIIa inhibition.

Conclusion

The present communication is an attempt to indentify the structural features of amidinophenylurea derivatives which are required for inhibition of factor VIIa. The study showed that presence of electron releasing groups are important for inhibition of factor VIIa, thus the generated QSAR model and pharmacophoric hypothesis can be used to design potent factor VIIa inhibitors.

Acknowledgement

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